UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/415,795	10/08/1999	PENGBO ZHOU	HMV-043.01	5319

25181 7590 10/03/2003

FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	26

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/415,795	ZHOU ET AL.	
	Examin r	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,16-36,39 and 41-56* is/are pending in the application.

4a) Of the above claim(s) *12,13,16-35 and 50-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 39, 41-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed May 22, 2003 canceling claims 37, 38 and 40 and amending claims 36, 41-45 and 47 has been entered.

Claims 12, 13, 16-36, 39 and 41-56 are pending. Claims 12, 13, 16-35 and 50-56 are withdrawn (Office action mailed November 19, 2002, pages 1 and 4). Claims 36, 39 and 41-49, species of SEQ ID NO:4, are under consideration.

Claim Objections

Claim 36, with dependent claims 39 and 41-49, is objected to because of the following: claim 36 has been amended to recite "WD40 domain" whereas the specification recites "WD domain". It is suggested that applicants maintain consistency through out the application and use the same term.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 44 has been amended to recite "F-box is at least 95% identical to a contiguous polypeptide" (emphasis added). The Examiner is unable to locate adequate support in the specification for percent identity of 95%. Thus there is no indication that F-box with at least 95% identity to a contiguous polypeptide was within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 36, 39 and 41-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims recite a genus of hybrid polypeptides comprising F-box and a WD40 domain and a target interaction domain.

"F-box polypeptides that further comprise a WD domain" encompass proteins of diverse structures and, in many cases, unknown function. Neither "F-box" nor "WD40 domain" is defined by structure.

The specification does not contain any disclosure of the structure and function of all hybrid polypeptides comprising F-box and a WD domain and a target interaction domain. The genus of hybrid polypeptides that comprise these above molecules is a large variable genus comprising many different proteins. Therefore, many structurally and functionally unrelated F-box and a WD domain and hybrid polypeptides are encompassed within the scope of these claims. The specification discloses only a three species of the claimed genus, hybrid of Cdc4 with LTP and E7N and a hybrid of βTrCP fused with E7N. In these cases, the known interaction domain was fused to a known component of a ubiquitin pathway and used for degrading a respective target. The specification fails to describe any other representative species by any identifying characteristics or properties other than being a *F-box* and a WD domain polypeptide and fails to provide any structure:function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 36, 39 and 41-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for targeting a target polypeptides using hybrid polypeptides comprising Cdc4/βTrCP and known target

polypeptide interaction domain, such as LTP and E7N, in yeast and human cells, respectively, does not reasonably provide enablement for a method of use of a hybrid comprising any F-box and a WD40 domain polypeptide for which target polypeptide and ubiquitin proteolysis pathway is unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claims 36, 39 and 41-49 are drawn to a method of use of any hybrid polypeptide comprising any F-box and a WD domain polypeptide and a target polypeptide interaction domain in any eukaryotic host cell. This amounts to any hybrid polypeptide comprising peptide structures both naturally-occurring and man-made. Polypeptides

comprising "F-box and a WD domain" encompass proteins of diverse structures and, in many cases, unknown function.

The art teaches that "F-box proteins directly contact ubiquitination substrates and can display selectivity in recognition of potential targets for ubiquitination, as would be expected of E3 proteins" (Skowyra et al., form PTO-1449 mailed November 14, 2000, reference AF, page 215, 2nd column). The art teaches the composition of *Saccharomyces cerevisiae* SCF ubiquitin ligase complex (ibid, for example).

However, ubiquitin proteolysis pathways are not yet elucidated in most settings. Without knowing the target interacting domain and its target as well as corresponding F-box protein, it is impossible to construct a requisite hybrid. Without knowing the pathway it is impossible to reconstitute it *in vitro*.

The specification teaches a method of use of a hybrid of Cdc4 with LTP and E7N for degrading pRB when both the hybrid and pRB were expressed in *S. cerevisiae* Y81 cells (page 135). The specification further teaches a method of use of a hybrid of a human analog of Cdc4, βTrCP, fused with E7N for degrading the endogenous protein, p107, that is human pRB analog, when expressed in human C33A cells (pages 138-139, Figure 11, page 140). Therefore, the specification teaches a method of use of a F-box polypeptide, Cdc4, and its human analog, βTrCP, fused to a known target polypeptide interaction domain, for degrading of a known target polypeptide *in vivo* in isolated yeast and human cells, respectively.

The specification does not support the broad scope of the claims because of the following.

Despite knowledge in the art to produce hybrid proteins, the specification fails to provide guidance as to the composition and structure and function of components of other ubiquitin ligases that can be used in the claimed method other than Cdc4 and its human homolog. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. The specification teaches the use of Cdc4/βTrCP based hybrids in a host cell naturally containing other components of a ubiquitin ligase complex. The hybrid is cell specific, i.e., Cdc4 is used in yeast cells and βTrCP is used in human cells. It is unknown whether the method can be used in a bacterial cell, for example. The specification does not teach how to use a hybrid comprising E7 and LTP and a second component other than Cdc4 in cells containing no pRB or p107.

Therefore, one of ordinary skill in the art would require guidance, in order to degrade any target polypeptide by using a hybrid comprising any F-box and a WD domain polypeptide in any cell other than a hybrid based on Cdc4 and βTrCP and known target polypeptide interaction domain in yeast and human host cell, respectively, in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Claim 45 is further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a hybrid protein comprising F-box and a WD domain polypeptide of SEQ ID NO: 4, does not reasonably provide enablement for a hybrid protein comprising F-box polypeptide encoded by a DNA that hybridizes to SEQ ID NO:3 under medium hybridization conditions comprising 0.2 x SSC at 50° C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of F-box polypeptides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of a single F-box and a WD domain polypeptide having the amino acid sequence of SEQ ID NO: 4.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claim which encompasses any F-box polypeptide encoded by a DNA that hybridizes to SEQ ID NO:3 under hybridization conditions comprising 0.2 x SSC at 50° C because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting F-box activity; (B) the general tolerance of F-box polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any F-box polypeptide residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any F-

box polypeptide encoded by a DNA that hybridizes to SEQ ID NO:3 under medium hybridization conditions comprising 0.2 x SSC at 50° C. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of F-box polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36, 39 and 41-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 recites "F-box" and "WD40 domain" polypeptide. There is no clear definition of terms "F-box", "WD40 domain" or "WD domain" either in the art or in the specification. This renders the metes and bounds of the claim unascertainable. Claims 39 and 41-49 are rejected as dependent from claim 36.

Claim 36 recites "a hybrid polypeptide comprised of F-box and a WD40 domain and a target polypeptide interaction domain". It is unclear whether F-box and a WD40 domain comprise one part of a hybrid protein or said hybrid protein can comprise three

separate parts such as F-box, WD40 domain and a target polypeptide interaction domain. Amending the claim to recite "a hybrid polypeptide comprising a recruitment domain, said domain comprising F-box and a WD domain, and a target polypeptide interaction domain", for example, is suggested (e.g., see page 9, penultimate paragraph). Further, claims 41-45 are unclear as reciting "wherein the F-box is from an F-box polypeptide" of SEQ ID NO:4. This can read on an undefined part (F-box) of the entire F-box polypeptide such as SEQ ID NO:4 while it appears that the recitation of "a polypeptide comprising F-box and a WD40 domain" is intended.

Claim 39 is incomplete as dependent from canceled claim 38.

Claim 41 recites "beta TrCPp". It is unclear which molecules other than SEQ ID NO:4 are encompassed by the claim.

Claims 46 and 47 are unclear for reciting "in vitro" and "in vivo". These terms are not specifically defined in the specification. While term "*in vivo*" can encompass a live organism, the specification teaches *in vivo* ubiquitination in *S. cerevisiae* INVSc1 cells (page 142). Therefore, in agreement with the specification, "in vivo" is construed as limited to isolated cells. The difference in scope of claims 46 and 47 is unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36, 39, 46, 48 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheffner et al.

Scheffner et al. (form PTO-1449 mailed January 28, 2002 reference BF) teach degradation of the retinoblastoma protein by human papilloma virus type 16 (HPV-16) E7-E6 fusion proteins *in vitro*.

Scheffner et al. teach that HPV-16 E7 contains the binding domain for the retinoblastoma gene product pRB and p107 (page 2425, 2nd column).

Absent clear definition of "F-box polypeptide", E6 is construed as F-box polypeptide.

Therefore, Scheffner et al. anticipate claims 36, 39, 46, 48 and 49.

Response to Arguments

Applicant's arguments filed May 22, 2003 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, written description rejection, Applicants argue that "F-box polypeptides contemplated in this invention (as indicated in the rejected claims) are F-box containing proteins that are members of the SCF" (Remarks, page 3, last paragraph). This is not persuasive because the claims are not limited to

the members of SCF family. Applicants further argue that "A discussion of the structural determinants of an F-box are also provided in the specification. Page 31, lines 3-24 of the specification provides a functional and structural description of an F-box" (page 4). This is not persuasive because page 31, lines 3-24, describes the location of WD domains in SEQ ID NO:4.

With regard to the 112, 1st paragraph, enablement rejection, Applicants argue that "contrary to the Examiner's statement, βTrCP is not the human homolog of pCdc4" (page 5, last paragraph and page 6, last paragraph). This is contradictory to the specification on page 138, for example, where it is taught that βTrCP is the human homolog of pCdc4. "Regarding target proteins, Applicants submit that the specification provides working examples of three different target proteins: pRb, p107 and the viral protein E2" (page 5, last paragraph). This is not persuasive, because three individual proteins with different properties do not adequately enable the entire scope comprising indefinite number of proteins. With regard to claim 44 (the rejection is similar to the current rejection of claim 45), Applicants argue that "the disclosure provided on page 27, lines 23-30 and page 28, lines 1-11, provides guidance as to which amino acids are considered conservative and would therefore be unlikely to affect protein function (page 8). This is not persuasive because while methods for determining percent homology are known and the specification considers various groups of amino acids

(e.g., page 27, 1st paragraph), the specification does not teach where in the structure the changes can be made without affecting the function.

With regard to the 112, 2nd paragraph, rejection, of claim 41, Applicants argue that "e.g., molecules from species other than human are encompassed by the claim" in relation to βTrCPp. This is not persuasive because Applicants do not indicate the support for such definition which is confusing as it would include such molecules as pCdc4 that was clearly not intended by the specification (e.g., page 138).

With regard to 112, 2nd paragraph, rejection of claims 46 and 47, claim 46 is rejected because, as explained above, its scope is unclear in view of the apparent scope of claim 47.

With regard to the 102(b) rejection of claims 36, 39, 46, 48 and 49, Applicants argue that "as stated in the specification, page 7, lines 3-19), the E6-AP genes belong to the HECT family of E3 proteins. The HECT protein ligase family is distinct from SCF family of E3 proteins, which include F-box polypeptides. As set forth above, F-box is clearly defined in the specification and does not include E6" (page 10). This is not persuasive because the claims are not drawn to SCF family members. Further, page 7, lines 3-19, does not mention E6-AP. However, page 6, last paragraph, teaches E6-AP as a member of HECT ubiquitin ligases. The specification teaches that SCF and HECT ubiquitin ligases are structurally related (page 6, last paragraph). Since the

specification does not structurally define F-box, it is deemed improper to exclude E6-AP from the scope of the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

September 30, 2002